

**Day-to-day blood pressure variability and risk of dementia in a general Japanese elderly population: the Hisayama
Study**

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Hazard ratios for the development of all-cause dementia and its subtypes according to CoV levels of home diastolic blood pressure, 2007-2012

CoV levels (%)	No. of events	No. of participants	Age- and sex-adjusted	HR (95% CI)	
				Model 1	Model 2
All-cause dementia					
Q1 (≤ 4.83)	21	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	37	419	1.65 (0.97-2.83)	1.62 (0.94-2.78)	1.65 (0.96-2.83)
Q3 (6.00-7.60)	56	419	2.08 (1.26-3.45)	2.09 (1.26-3.48)	2.13 (1.28-3.54)
Q4 (≥ 7.61)	80	418	2.75 (1.69-4.46)	2.72 (1.67-4.43)	2.73 (1.68-4.44)
<i>P</i> for trend			<0.001	<0.001	<0.001
Vascular dementia					
Q1 (≤ 4.83)	14	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	25	419	2.39 (0.75-7.62)	2.58(0.80-8.32)	2.95 (0.91-9.57)
Q3 (6.00-7.60)	39	419	2.95 (0.96-8.99)	3.12 (1.01-9.59)	3.51 (1.13-10.91)
Q4 (≥ 7.61)	56	418	3.67 (1.24-10.88)	3.39 (1.14-10.07)	3.57 (1.19-10.68)
<i>P</i> for trend			0.02	0.03	0.03
Alzheimer's disease					
Q1 (≤ 4.83)	4	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	10	419	1.66 (0.87-3.20)	1.60 (0.82-3.09)	1.60 (0.82-3.10)
Q3 (6.00-7.60)	14	419	2.09 (1.13-3.87)	2.05 (1.11-3.81)	2.05 (1.10-3.81)
Q4 (≥ 7.61)	19	418	2.79 (1.54-5.03)	2.87 (1.59-5.19)	2.87 (1.59-5.19)
<i>P</i> for trend			<0.001	<0.001	<0.001

CoV indicates the coefficient of variation; HR, hazard ratio; and CI, confidence interval.

Model 1 was adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, and regular exercise.

Model 2 was adjusted for the covariates included in model 1 plus the mean values of home diastolic blood pressure for 4 weeks.

Supplemental Table 2. Hazard ratios for the development of all-cause dementia and its subtypes according to SD, MMD, ARV, and VIM levels of home systolic blood pressure, 2007-2012

Levels of variability	All-cause dementia		Vascular dementia		Alzheimer's disease	
	No. of events/ No. of participants	HR(95%CI)	No. of events/ No. of participants	HR(95%CI)	No. of events/ No. of participants	HR(95%CI)
SD (mmHg)						
Q1 (≤ 6)	23/418	1.00 (reference)	3/418	1.00 (reference)	17/418	1.00 (reference)
Q2 (7-8)	35/419	1.21 (0.71-2.05)	9/419	2.37 (0.64-8.85)	23/419	1.07 (0.57-2.02)
Q3 (9-10)	49/419	1.52 (0.91-2.53)	11/419	2.52 (0.68-9.28)	34/419	1.39 (0.76-2.53)
Q4 (≥ 11)	87/418	2.22 (1.35-3.65)	24/418	3.95 (1.12-13.86)	60/418	2.17 (1.20-3.91)
<i>P</i> for trend		<0.001		0.02		0.003
MMD (mmHg)						
Q1 (≤ 26.99)	24/410	1.00(reference)	4/410	1.00 (reference)	17/410	1.00 (reference)
Q2 (27.00-34.50)	36/426	1.07(0.63-1.80)	7/426	1.27 (0.37-4.40)	27/426	1.12 (0.61-2.07)
Q3 (34.67-42.66)	45/413	1.38(0.83-2.29)	13/413	2.26 (0.71-7.15)	28/413	1.23 (0.66-2.27)
Q4 (≥ 42.67)	89/425	1.89(1.16-3.08)	23/425	2.65 (0.86-8.12)	62/425	1.87 (1.04-3.35)
<i>P</i> for trend		0.002		0.03		0.02
ARV (mmHg)						
Q1 (≤ 6.41)	26/417	1.00 (reference)	4/417	1.00 (reference)	18/417	1.00 (reference)
Q2 (6.42-8.09)	34/420	1.03 (0.61-1.72)	10/420	1.52 (0.47-4.92)	24/420	1.19 (0.67-2.13)
Q3 (8.10-10.17)	51/419	1.44 (0.88-2.34)	15/419	2.15 (0.69-6.73)	32/419	1.19 (0.67-2.09)
Q4 (≥ 10.18)	83/418	1.75 (1.08-2.84)	18/418	1.66 (0.52-5.31)	60/418	2.08 (1.23-3.51)
<i>P</i> for trend		0.005		0.44		0.004
VIM (units)						
Q1 (≤ 6.67)	30/418	1.00(reference)	8/418	1.00 (reference)	20/418	1.00 (reference)
Q2 (6.68-8.11)	39/419	1.21(0.75-1.96)	9/419	1.31 (0.50-3.44)	27/419	1.19 (0.67-2.13)
Q3 (8.12-9.90)	50/419	1.37(0.87-2.16)	14/419	1.70 (0.71-4.12)	31/419	1.19 (0.67-2.09)
Q4 (≥ 9.91)	75/418	1.97(1.27-3.05)	16/418	1.93 (0.81-4.60)	56/418	2.08 (1.23-3.51)

<i>P</i> for trend	0.001	0.11	0.004
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SD indicates standard deviation; MMD, maximum and minimum differences; ARV, average real variability; VIM, variability independent of the mean; HR, hazard ratio; and CI, confidence interval.

Adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise, and mean values of home systolic blood pressure for 4 weeks.

Supplemental Table 3. Baseline characteristics of subjects according to mean values of home systolic blood pressure levels, the Hisayama Study, 2007

Variables	Quartile of mean systolic blood pressure levels (mmHg)				<i>P</i> for trend
	Q1 (≤ 125) n=418	Q2 (126-136) n=419	Q3 (137-150) n=419	Q4 (≥ 151) n=418	
Age, mean (SD), y	69 (7)	70 (7)	72 (7)	74 (8)	<0.001
Women, %	62.2	55.1	52.7	53.6	0.009
Education \leq 9 years, %	37.4	40.4	47.8	48.3	<0.001
Systolic blood pressure, mean (SD), mmHg	116 (7)	131 (3)	143 (4)	161 (10)	<0.001
Diastolic blood pressure, mean (SD), mmHg	70 (6)	76 (7)	80 (8)	84 (9)	<0.001
Use of antihypertensive agents, %	17.0	41.1	53.5	61.7	<0.001
Electrocardiogram abnormalities, %	11.0	14.8	22.7	31.1	<0.001
Diabetes mellitus, %	13.4	20.3	23.9	28.0	<0.001
Serum total cholesterol, mean (SD), mmol/L	5.49 (0.89)	5.44 (0.97)	5.25 (0.89)	5.33 (0.87)	<0.001
Body mass index, mean (SD), kg/m ²	21.8 (3.0)	23.2 (3.3)	23.6 (3.3)	23.6 (3.5)	<0.001
History of cardiovascular disease, %	5.3	6.9	9.1	10.8	0.002
Smoking habits, %	12.2	10.0	14.6	15.3	0.06
Alcohol intake, %	36.6	40.8	45.1	47.0	0.001
Regular exercise \geq 3 times/w, %	14.1	15.3	15.8	11.5	0.34
MMSE score, mean (SD)	27.5 (2.4)	27.5 (2.1)	27.5 (2.2)	27.4 (2.2)	0.50

SD indicates standard deviation; and MMSE, Mini-Mental State Examination.

Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3. MMSE was examined in 2005-2006 in 1,030 participants.

Supplemental Table 4. Association between mean values of home systolic blood pressure levels and the development of all-cause dementia and its subtypes, 2007-2012

Mean systolic blood pressure levels (mmHg)	Person-years at risk	No. of events	Incidence rates (per 10 ³ person-years)*	HR (95% CI)		
				Age- and sex-adjusted	Model 1	Model 2
All-cause dementia						
Q1 (≤ 125)	1916	32	16.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	35	16.2	0.92 (0.57-1.48)	0.88 (0.54-1.44)	0.78 (0.46-1.30)
Q3 (137-150)	1800	55	30.6	1.14 (0.73-1.77)	1.02 (0.64-1.64)	0.91 (0.56-1.48)
Q4 (≥ 151)	2321	72	31.0	1.08 (0.70-1.67)	0.98 (0.61-1.56)	0.81 (0.50-1.32)
<i>P</i> for trend				0.52	0.88	0.58
Vascular dementia						
Q1 (≤ 125)	1916	5	2.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	6	2.8	1.00 (0.30-3.27)	1.08 (0.32-3.64)	1.22 (0.35-4.27)
Q3 (137-150)	1800	15	8.3	2.05 (0.74-5.70)	2.29 (0.78-6.70)	2.08 (0.67-6.45)
Q4 (≥ 151)	2321	21	9.0	2.29 (0.84-6.28)	2.55 (0.88-7.42)	2.26 (0.72-7.10)
<i>P</i> for trend				0.04	0.03	0.10
Alzheimer's disease						
Q1 (≤ 125)	1916	25	13.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	26	12.0	0.88 (0.51-1.53)	0.83 (0.47-1.45)	0.70 (0.39-1.25)
Q3 (137-150)	1800	34	18.9	0.89 (0.53-1.51)	0.79 (0.45-1.37)	0.68 (0.38-1.20)
Q4 (≥ 151)	2321	49	21.1	0.90 (0.54-1.49)	0.78 (0.45-1.33)	0.62 (0.35-1.08)
<i>P</i> for trend				0.75	0.41	0.14

HR indicates hazard ratio; and CI, confidence interval.

Model 1 was adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, and regular exercise.

Model 2 was adjusted for the covariates included in model 1 plus the Mini-Mental State Examination score in 2005-2006 (n=1030).

*The values are unadjusted.

Supplemental Table 5. Multivariable-adjusted hazard ratios of dementia per 1-SD increment in CoV of home systolic blood pressure in various subgroups of the study population, 2007-2012

Subgroups of variables	No. of events	No. of participants	HR (95% CI) per 1-SD increment in CoV of home systolic blood pressure (1 SD=3.11%)	P for interaction
All-cause dementia				
Sex				
Men	72	738	1.31 (1.10-1.56)	
Women	122	936	1.24 (1.06-1.45)	0.46
Age (years)				
60-74	58	1145	1.23 (1.00-1.51)	
≥75	136	529	1.31 (1.14-1.50)	0.93
Diabetes mellitus				
No	149	1315	1.31 (1.15-1.49)	
Yes	44	358	1.22 (0.96-1.55)	0.27
Use of antihypertensive agents				
No	90	949	1.24 (1.04-1.48)	
Yes	104	725	1.27 (1.08-1.48)	0.69
Smoking habits				
No	172	1456	1.27 (1.13-1.44)	
Yes	22	218	1.19 (0.80-1.79)	0.79
Vascular dementia				
Sex				
Men	24	738	1.14 (0.83-1.58)	
Women	23	936	1.09 (0.74-1.62)	0.88
Age (years)				
60-74	17	1145	1.21 (0.83-1.76)	
≥75	30	529	0.99 (0.72-1.37)	0.35
Diabetes mellitus				
No	34	1315	1.08 (0.81-1.45)	
Yes	13	358	1.18 (0.75-1.83)	0.92

Use of antihypertensive agents				
No	21	949	0.88 (0.57-1.35)	
Yes	26	725	1.20 (0.87-1.65)	0.78
Smoking habits				
No	39	1456	1.11 (0.84-1.47)	
Yes	8	218	1.93 (0.34-10.96)	0.72
Alzheimer's disease				
Sex				
Men	41	738	1.40 (1.11-1.76)	
Women	93	936	1.30 (1.08-1.55)	0.43
Age (years)				
60-74	37	1145	1.18 (0.90-1.55)	
≥75	97	529	1.44 (1.23-1.69)	0.37
Diabetes mellitus				
No	106	1315	1.36 (1.16-1.58)	
Yes	28	358	1.32 (0.98-1.77)	0.52
Use of antihypertensive agents				
No	64	949	1.34 (1.09-1.64)	
Yes	70	725	1.32 (1.10-1.59)	0.79
Smoking habits				
No	121	1456	1.36 (1.18-1.57)	
Yes	13	218	1.00 (0.59-1.70)	0.36

SD indicates standard deviation; CoV, coefficient of variation; HR, hazard ratio; and CI, confidence interval.

The HRs were adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise and mean values of home systolic blood pressure for 4 weeks. The variable relevant to the subgroup was excluded from each model.

Supplemental Table 6. Baseline characteristics of subjects according to CoV levels of home systolic blood pressure, the Hisayama Study, 2007 (n=1030)

Variables	All n=1030	Quartile of CoV levels (%)				<i>P</i> for trend
		Q1 (≤ 5.32) n=257	Q2 (5.33-6.41) n=258	Q3 (6.42-7.79) n=258	Q4 (≥ 7.80) n=257	
Age, mean (SD), y	75 (6)	74 (6)	75 (5)	76 (6)	76 (6)	<0.001
Women, %	57.4	46.7	58.5	62.0	62.3	<0.001
Education \leq 9 years, %	51.6	50.2	50.8	50.8	54.7	0.34
Systolic blood pressure, mean (SD), mmHg	141 (18)	140 (18)	141 (18)	143 (18)	141 (17)	0.35
Diastolic blood pressure, mean (SD), mmHg	77 (9)	77 (9)	77 (10)	77 (9)	76 (9)	0.16
Use of antihypertensive agents, %	50.7	51.0	50.8	46.1	54.9	0.62
Electrocardiogram abnormalities, %	21.8	22.2	23.6	18.2	23.4	0.87
Diabetes mellitus, %	22.8	21.4	24.8	23.3	21.9	0.99
Serum total cholesterol, mean (SD), mmol/L	5.26 (0.87)	5.23 (0.82)	5.26 (0.83)	5.28 (0.92)	5.26 (0.91)	0.74
Body mass index, mean (SD), kg/m ²	22.9 (3.4)	22.9 (3.3)	23.2 (3.4)	22.9 (3.4)	22.6 (3.3)	0.19
History of cardiovascular disease, %	9.2	7.4	7.8	9.3	12.5	0.04
Smoking habits, %	10.8	14.4	7.4	9.7	11.7	0.50
Alcohol intake, %	37.4	41.3	34.1	37.2	37.1	0.49
Regular exercise \geq 3 times/w, %	13.7	16.3	15.5	11.6	11.3	0.05
MMSE score, mean (SD)	27.3 (2.3)	27.7 (2.2)	27.7 (2.0)	27.3 (2.3)	27.2 (2.2)	0.005

CoV indicates the coefficient of variation; SD, standard deviation; and MMSE, Mini-Mental State Examination.

Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3.

MMSE was examined in 2005-2006.

Supplemental Table 7. Association between CoV levels of home systolic blood pressure and the development of all-cause dementia and its subtypes after including pre-baseline cognitive assessment in the analyses (n=1030), 2007-2012

CoV levels (%)	Population at risk	No. of events	HR (95% CI)
			Multivariable-adjusted*
All-cause dementia			
Q1 (≤ 5.07)	223	23	1.00 (reference)
Q2 (5.08-6.21)	249	31	1.18 (0.69-2.04)
Q3 (6.22-7.59)	271	46	1.34 (0.81-2.23)
Q4 (≥ 7.60)	287	80	2.27 (1.42-3.65)
<i>P</i> for trend			<0.001
Vascular dementia			
Q1 (≤ 5.07)	223	4	1.00 (reference)
Q2 (5.08-6.21)	249	8	2.01 (0.59-6.89)
Q3 (6.22-7.59)	271	11	2.34 (0.72-7.64)
Q4 (≥ 7.60)	287	20	3.74 (1.23-11.38)
<i>P</i> for trend			0.01
Alzheimer's disease			
Q1 (≤ 5.07)	223	17	1.00 (reference)
Q2 (5.08-6.21)	249	21	1.08 (0.56-2.05)
Q3 (6.22-7.59)	271	30	1.09 (0.60-2.00)
Q4 (≥ 7.60)	287	57	2.16 (1.24-3.75)
<i>P</i> for trend			0.002

CoV indicates the coefficient of variation; HR, hazard ratio; and CI, confidence interval.

*Adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise, and Mini-Mental State Examination score in 2005-2006.